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LETTER TO THE EDITOR

Guillain-Barré syndrome, SARS-CoV-2 and molecular mimicry

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We read with great interest the report by Keddie and colleagues[1] on the absence of epidemiological evidence of an association between SARS-CoV-2 and Guillain-Barré syndrome (GBS) in the UK between January and June 2020.

Nevertheless, the additional proteomic analysis presented in the article appears to be problematic. An alignment analysis between viral and human proteins was carried out with the National Centre for Biotechnology Information (NCBI's) Basic Local Alignment Search Tool (BLAST). BLAST is useful to infer functional and evolutionary relationships between proteins and it is commonly applied to characterize newly determined sequences, but it might draw an incomplete picture of peptide sharing of immunological relevance because it might miss identical amino acid sequences shared by non-homologous regions of the compared proteins.[2,3] The BLAST parameters include indeed an 'expect value threshold' that is meant to correct for possible matches due to chance.[2] Although this correction is necessary when comparing protein sequences for homology and biological relationship, it has to be set arbitrarily and might discard matches that do not reflect an evolutionary relationship between organisms and proteins but nevertheless can be related to cross-reactive immunological phenomena. The stringency of such analysis also depends on other parameters that are chosen.

The authors found that: 'SARS-CoV-2 proteins including the spike/surface, envelope, membrane and nucleocapsid phosphoprotein have no significant similarity with any referenced human protein' with the exception of a pentapeptide (VVVNA) that is present in both the viral ORF1ab/ORF1a polyprotein and the human mono-ADP-ribosyltransferase (PARP14).

A different approach consists in dissecting the primary amino acid sequence of the viral proteins in oligopeptides with a sliding window of one residue (i.e. maximum degree of overlap between contiguous oligopeptides) and to check the human proteomes for exact matches of such oligopeptides.[4] Our and other research groups have identified with this approach a variety of hexapeptides that are shared (i.e. identical) between the SARS-CoV-2 proteins and the human proteome, with a potential relevance for immune cross-reactivity and specifically for GBS pathogenesis.[4-8] Moreover, sequence similarity between SARS-CoV-2 and human GBS-related proteins was even found with BLAST, and this can possibly be explained by parameter setting differences.[9]

Of course, protein sequence comparisons do not take into account two other potential targets of cross-reactivity: non-peptidic and discontinuous protein epitopes, but this approach would go beyond the intended purpose of the analysis presented by Keddie and colleagues.[1]

The methodological issue that we describe here should be pointed out, but may not necessarily affect the conclusion of the paper on the lack of definitive evidence of a link between COVID-19 and GBS, and we do agree with the authors that further basic and clinical research is needed to possibly turn the absence of evidence into actual evidence of absence.[10]

Data availability

The data that support this work were made available in their entirety in the articles referenced in the main text.

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Competing interests

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